by feeding the immunoreceptive [animal] mammal with a substance comprising a physiologically acceptable plant material containing the NEPA from a transgenic plant expressing the NEPA to cause a secondary immune response to oral administration specific to the NEPA stronger than a response specific to NEPA caused by the NEPA in the absence of prior immunizing [where the animal is made immunoreceptive to the NEPA by immunization against a non-enteric pathogen containing the NEPA prior to feeding the animal the substance].

Please amend Claim 2 as follows:

Claim 2 (amended)

The method of Claim 1 where the mammal is a human [where the NEPA is HBsAg]

Please rewrite Claim 3 as follows:

Claim 3 (amended)

[A] The method of Claim 2 wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those that cause hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue hemoragic fever, tetanus, ~~staphylococcus aureous~~, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever [for boosting an immune response to a non-enteric pathogen in a human previously having a positive response to primary immunization against the pathogen which method comprises the human ingesting a substance comprising a physiologically acceptable plant material containing an NEPA contained in the pathogen].

Please rewrite Claim 4 as follows:

Claim 4 (amended)

The method of Claim 3 wherein the non-enteric pathogen is hepatitis B and the NEPA is hepatitis B surface antigen (HBsAg).

Please amend Claim 8 as follows:

Claim 8 (amended)

The method of Claim 6 wherein the human ingests sufficient plant material to provide from about 10 to about 100 micrograms of hepatitis B surface antigen(HBsAg) per kilogram of body weight.

In Claim 16, please replace "*solanaceae*" with --*Solanaceae*--.

In Claim 17, please replace "*solanaceae*" with --*Solanaceae*--.

Remarks

Claims 1-4, 8 and 16-19 have been rejected under 35 U.S.C. 112 for being indefinite. The rejection should be withdrawn.

All rejections under 35 U.S.C. 112 have been overcome by amendment or by the following arguments.

The Examiner states that that "providing an immune response" is indefinite. With due respect to the Examiner, the phrase is not indefinite. A term that is generic is not the same as a term that is indefinite. (See MPEP 2173.04). One skilled in the art knows how to determine the types of immune response listed by the Examiner and there is no reason that the invention should be restricted to any one of them. None of the claims are indefinite. In any case the claims have

now been amended so that they are restricted to secondary immune response. This amendment would overcome the Examiner's objection in any case.

The Examiner states that the phrase "wherein the animal is made immunoreceptive to HBsAg" is indefinite on the ground that "immunoreceptive is not an art recognized term. In the first place, the phrase cited by the Examiner does not appear in the claims. It is assumed that the Examiner means NEPA rather than HBsAg. Secondly it would be clear to one skilled in the art what the term means. The Examiner has clearly understood the term and has apparently objected to it more on the basis of breadth than ambiguity. The amendments to the claims have removed any problem with the phrase since the claims are now restricted to making the mammal immunoreceptive by prior immunization.

Claims 2, 4, and 8 have been objected to because of the use of the abbreviation HBsAg. This term is defined in the specification and is art recognized. There is no ambiguity. In any case, the claims have been amended rendering the objection moot.

The objection to Claim 3 for lack of antecedent basis for pathogen is not understood. Antecedent basis for the term was supplied in line 1. In any case the claim has now been amended so that it is dependent on Claim 1 rendering the objection moot.

The objection with respect to "NEPA" in Claim 3 has been rendered moot by amendment.

The objection to Claim 3 on the ground that the term "physiologically acceptable plant material containing an NEPA contained in the pathogen" is vague should be withdrawn. The meaning is clear as evidenced by the Examiner's suggestion of alternative language. In any case

language similar to that suggested by the Examiner has been added by amendment. The objection should also be withdrawn for that reason.

The Examiner states that all of the claims are made vague by the phrase "providing an immune response to a non-enteric pathogen antigen", and by the phrase "where an animal is immunoresponsive to the NEPA" because there is no definite delineation between the phrases. The objection is not understood. It is clear from the context of the claims that the "providing an immune response" is by an animal that is primed to have such a response , i.e. is made immunoreceptive so that a further response can be had by oral challenge. From the discussion by the Examiner, he clearly understands the language to mean just that and any problem he is having seems to be related to breadth of the terms not ambiguity. In any case the amendments have added even more clarity and have limited the claims to rendering the mammal immunoreceptive by vaccination. The rejection should be withdrawn.

With due respect to the Examiner, having a healthy immune system does not necessarily mean that an individual is immunoreceptive to an antigen no matter how it is presented. There are many antigens that raise an immune response when injected that do not raise an immune response when presented orally. The present invention employing a prior vaccination permits an immune response to be raised to an antigen that is presented orally when such an antigen presented orally would not normally raise such a response.

The rejections with respect to Claim 16 and 17 are not understood. *Solanaceae* is a Latin term for a family in biological classification and is properly italicized. There is no ambiguity. If

the rejection was based upon whether or not the term was capitalized or italicized or underlined, this would be a formal objection and would hardly support a rejection under 35 U.S.C. 112.

The objection that Claims 18 and 19 are substantial duplicates should be withdrawn. They are not and never were substantial duplicates. Original Claim 19 required the NEPA to be HBsAg. Original Claim 18 did not. The claims have now been further amended placing even further demarcation between Claims 18 and 19.

Claims 1, 3, 5-7 and 9-19 have been rejected under 35 U.S.C. 103 as being unpatentable over U.S. Patent 5,935,570 to Koprowski et al. in view of Stites et al.

This rejection should be withdrawn.

Koprowski et al., contrary to statements by the Examiner, does not disclose or suggest feeding a plant material containing NEPA expressed by the plant as required by the present claims. The Koprowski et al. plant material is not genetically altered as asserted by the Examiner. The plants of Koprowski et al. are simply hosts for a parasitic microorganism expressing a bioactive compound (and as such the plants would not usually grow happily). The only specific example in Koprowski et al. is for a microorganism that expresses a gene for rabies N protein. Since rabies is known to have the ability to invade a mammal by means other than through a breach in the skin and can raise an immune response enterically without an adjuvant or prior immunization, as evidenced by Koprowski, it is not covered by the present claims since it does not meet the criteria for non-enteric pathogens in the claims.

Koprowski et al. suggest that their method has wide application, e.g. for treatment of viral infections, bacterial infections, fungal infections, protozoan infections, diabetes, immune

disorders, cancer and heart disease. Koprowski et al. more specifically suggest that their method could be used for mucosal pathogens, e.g. rabies, respiratory syncytial virus, cholera. typhoid fever, herpes simplex types I and II, tuberculosis, pathogenic pneumococci, human immunodeficiency virus-1 (HIV-1) and human immunodeficiency virus-2 (HIV-2).

The only specific example given is for rabies. There is no enablement for the other suggested applications. If the disclosure actually enabled everything suggested, oral vaccines effective against Aids, cancer, and herpes, among many others, would be made available simply by following the teachings of the Koprowski et al patent. This is simply not the case.

Koprowski et al. certainly does not enable or even reasonably suggest application for orally raising an immune response to antigens of the non-enteric pathogens in accordance with the method of the present claims. Koprowski et al. does not disclose or suggest making the mammal immunoreceptive by prior vaccination as required by the present claims. Nor does Koprowski suggest any way in which an antigen from a non-enteric pathogen, that would normally not raise an immune response when ingested orally, can be made to do so. It is completely unobvious in view of Koprowski et al. that oral administration of an antigen that would normally not raise an immune response, can be made to do so by prior immunization. The Examiner's statement that the result would be obvious is unfounded upon the reference, is gratuitous and is classic hindsight.

There is no suggestion or teaching that prior immunization would have would have any effect whatsoever **upon oral immune response to antigens** of the non-enteric pathogens in the present claims and there is no suggestion that such prior immunization would have any effect

upon an antigen that is expressed by and often contained within the structure of plant material. Stites et al. adds nothing to cure the inadequate teachings and suggestions of Koprowski et al. Stites does not suggest anything whatsoever concerning orally effective vaccines against non-enteric pathogens as presently claimed and certainly suggests nothing suggesting that an NEPA would orally raise a highly effective immune response in the presence of a suitable adjuvant as presently claimed.

Stites et al. adds nothing to cure the inadequate teachings and suggestions of Koprowski et al. Stites does not suggest anything whatsoever concerning orally effective vaccines against non-enteric pathogens as presently claimed and certainly suggests nothing suggesting that an NEPA, that is not normally effective orally, would orally raise a highly effective immune response if there is a prior immunization to the antigen.

The rejection should be withdrawn.

Claims 1-2 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,914,123 to Arntzen et al. in view of Stites et al. Basic and Clinical Immunology, pp. 723-741.

This rejection should be withdrawn.

Arntzen et al. teaches a method for making a transgenic plants, e.g. tobacco, tomato or potato that expresses antigens from certain pathogenic organism, especially HBsAg as set forth in the specific examples.

Arntzen et al. does not teach that ingestion of a tomato or potato (and certainly not the tobacco because it is toxic) would cause an immune response to HBsAg.

Arntzen et al. recognize that not all antigens would cause an immune response if ingested.

Arntzen et al. says in column 15 beginning at line 27,

"The vaccines are conventionally administered parenterally, by injection, for example either subcutaneously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, ***in some cases***, oral formulations or aerosols." (emphasis added).

While Arntzen et al. suggest that tomato juice containing HBsAg might be used as a vaccine, in fact Arntzen provides no supporting data showing any immune response whatsoever to tomato juice or any other plant containing HBsAg. To the extent that Arntzen teaches that tomato juice or any other plant material containing HBsAg can be used as a vaccine, it is an inoperative reference since there is no teaching or suggestion as to how that might be done. ***Simply ingesting the plant material, as suggested by Arntzen et al., does not confer immunity***. There is good reason for Arntzen's omission of data showing immune response to HBsAg by ingesting food material containing it, since prior to the present invention, in fact, there was little if any immune response whatsoever to HBsAg in orally ingested tomato juice or any other plant expressing HBsAg. The response, if any, is clearly insufficient for that purpose.

Reference to the examples in the present specification clearly illustrates that priming of the subject of the immunization is required by either pre-vaccination or the use of an effective adjuvant and **pre-vaccination is required by the present claims**. Arntzen et al. suggests neither pre-vaccination nor an adjuvant. Arntzen et al. doesn't suggest prior immunization for any purpose whatsoever and certainly does not suggest that prior immunization would permits

the obtaining of a high immune response to an orally administered antigen, that would not normally give such a response, as required by the present claims.

Arntzen discloses or suggests no way in which a high immune response could be orally obtained.

In any case there is certainly no suggestion of the enhanced immune response to NEPA's in orally administered plant material expressing the NEPA, as provided by the method presently claimed.

Stites et al. adds nothing to cure the inadequate teachings and suggestions of Arntzen et al. Stites does not suggest anything whatsoever concerning orally effective vaccines against non-enteric pathogens as presently claimed and certainly suggests nothing suggesting that an NEPA as claimed would orally raise a highly effective immune response if the mammal has a prior immunization.

Claims 3-19 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,914,123 to Arntzen et al., and U.S. patent 5,935,570 to Koprowski et al. in view of Stites et al. Basic and Clinical Immunology, pp. 723-741.

This rejection should be withdrawn.

Arntzen et al. teaches a method for making a transgenic plants, e.g. tobacco, tomato or potato that expresses antigens from certain pathogenic organism, especially HBsAg as set forth in the specific examples.

Arntzen et al. does not teach that ingestion of a tomato or potato (and certainly not the tobacco because it is toxic) would cause an immune response to HBsAg.

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"The vaccines are conventionally administered parenterally, by injection, for example either subcutaneously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, ***in some cases***, oral formulations or aerosols." (emphasis added).

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There is good reason for Arntzen's omission of data showing immune response to HBsAg by ingesting food material containing it, since prior to the present invention, in fact, there was little if any immune response whatsoever to HBsAg in orally ingested tomato juice or any other plant expressing HBsAg. The response, if any, is clearly insufficient for that purpose.

Reference to the examples in the present specification clearly illustrates that priming of the subject of the immunization is required by either pre-vaccination or the use of an effective adjuvant. Arntzen et al. suggests neither pre-vaccination nor an adjuvant and **pre-vaccination is required by the present claims.** Arntzen et al. doesn't suggest prior immunization for any purpose whatsoever and certainly does not suggest that prior immunization would permits the

obtaining of a high immune response to an orally administered antigen, that would not normally give such a response, as required by the present claims.

Arntzen discloses or suggests no way in which a high immune response could be orally obtained.

In any case there is certainly no suggestion of the enhanced immune response to NEPA's in orally administered plant material expressing the NEPA, as provided by the method presently claimed.

The Examiner states that Koprowski "teaches a method for genetically altering the plant material of solanaceous plants..." The Examiner's statement is inaccurate. Koprowski at al. does not teach or suggest any method for making a transgenic plant but teaches a microorganism expressing a bioactive compound, e.g. an immunogenic rabies polypeptide. The microorganism may then be used to infect a plant as a parasite but does not alter the genetic character or expression of the plant. Further, Koprowski does not suggest pre-immunization for any purpose and certainly not for obtaining an oral immune response from an antigen that would not normally give an oral immune response. Koprowski et al. therefore does not cure any of the critical defects of Arntzen et al.

Stites et al. adds nothing to cure the inadequate teachings and suggestions of Koprowski et al. and Arntzen et al. Stites does not suggest anything whatsoever concerning orally effective vaccines against non-enteric pathogens as presently claimed and certainly suggests nothing suggesting that an NEPA, that is not normally effective orally, would orally raise a highly effective immune response if there is a prior immunization to the antigen.

None of the references, alone or in combination, enable or suggest the raising of an oral immune response to NEPA of a non-enteric pathogen as defined in the present claims and **expressed in plants** and certainly do not suggest that an enhanced oral response to the NEPA could be obtained when the animal was pre-vaccinated.

The conflicts, same invention type double patenting, and obviousness type double patenting between the present application and Application numbers 09/420,695 and 09/464,416 have been removed by amendment.

It is requested that the rejections over copending application 09/418,177 be temporarily held in abeyance since application 09/418,177 is being allowed to go abandon by failure to respond. The rejections will thus be moot. In any case, the claims have been amended so that any conflict has been eliminated.

All rejections have been addressed and overcome by the foregoing amendments and remarks. It is therefore courteously requested that all rejections be withdrawn and all claims be allowed.

Respectfully submitted,

Dated:

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